Background and Physiology of Coagulation

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Objectives

- Understand the physiology of how a thrombosis is formed and dissolved within the body
  - Describe the role of platelets in forming a thrombosis
  - Describe the role of the coagulation cascade in forming a thrombosis
  - Be able to describe the natural processes by which clots are dissolved

Hemostatic Balance

Platelet Functions

- Adhesion
- Secretion
- Aggregation
- Fusion

Platelet Structure

Platelet Adhesion

- When subendothelial connective tissues are exposed in the blood, platelet adhere to that exposed tissue
- Subendothelial microfibrils bind to VWF, which then binds to GPIb binding site on the platelet
**Platelet Adhesion**

- After adhesion, platelets will change shape, extrude long pseudopods which enhance platelet interaction.
- Activated platelets adhere to exposed collagen by GPIIb and vWF.

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**Platelet Activation**

- Aggregation begins immediately, prompted by presence of fibrinogen binding to GPIIb/IIIa complex.
- Fibrinogen bridges form between adjacent platelets.
- Once exposed to collagen or thrombin, platelets will secret some of their granule contents (AFP, serotonin, fibrinogen, calcium).
- Activate prostaglandin synthesis, leading to production of thromboxane A2 (TXA2).
- Thromboxane A2 potentiates platelet aggregation and causes vasoconstriction.

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**Platelet/Endothelial Cell**

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**Platelet Aggregation**

- Once ADP and thromboxane A2 are released (during secretion), more platelets aggregate.
- ADP causes platelets to swell, adjacent platelet adhere to each other.
- Liberates more ADP and thromboxane A2, therefore causing positive feedback.
- Eventually build a platelet mass.
**Platelet Fusion**

- Irreversible platelet aggregation
- Thrombin encourages fusion
- Fibrin reinforces stability
- High concentrations of ADP, other enzymes released during secretion and platelet contractile proteins contribute to fusion

**Platelet Procoagulant Activity**

- The exposed phospholipid membrane on the activated platelet leads to:
  - Formation of factor Xa (through IXa, VIIIa, and X)
  - Formation of thrombin [from Xa, Va and prothrombin (II)]

**Role of coagulation cascade**

- A "biological amplification system" which ends in the generation of thrombin
- Thrombin converts fibrinogen into fibrin.
- Fibrin enmeshes the platelets and converts unstable platelet plugs to firm stable hemostatic plugs

**Coagulation Cascade**

[Diagram of the coagulation cascade showing intrinsic, extrinsic, and common pathways, illustrating the conversion of fibrinogen to fibrin and the involvement of various factors such as factor XII, factor XI, factor X, factor IX, factor VIII, and factor VIIa.]

**Coagulation Cascade**

[Diagram showing the coagulation cascade with a focus on the activation pathways and the role of inhibitors such as warfarin, unfractionated heparin, and protein C in preventing clot formation.]
When fibrinogen is hydrolyzed by thrombin, fibrin monomers are formed. These link to form a loose, insoluble fibrin polymer. Factor XIII is activated by thrombin and calcium, and helps stabilize the fibrin polymers with covalent bond cross links.

Tissue factor pathway inhibitor (tFPI) accumulates at site of injury. Inhibits Xa and VIIa and tissue factor. Antithrombin inactivates serine proteases by forming high molecular weight stable complexes. Protein C and Protein S: Protein C is activated when thrombin binds to endothelial cell surface receptor thrombomodulin. Protein C destroys factors Va and VIIIa. Protein S is a co-factor which facilitates binding of activated protein C to the platelet surface.

Fibrinolysis: Plasminogen is converted to plasmin primarily by tissue plasminogen activator (tPA). tPA is released from the endothelial cells. tPA binds to fibrin, and converts plasminogen in the thrombus to plasmin. Protein C protects tPA by destroying inhibitors of tPA. Plasmin digests fibrinogen, fibrin, factors V and VIII and others.
**Role of Endothelial Cells**

- Work to synthesize PGI2 and nitric oxide, which cause vasodilation and inhibit platelet aggregation
- Release tPA and activate fibrinolysis
- Synthesizes:
  - Tissue factor & its inhibitor (TFPI)
  - Prostacyclin
  - VWF
  - Plasminogen activator
  - Antithrombin and thrombomodulin

**Hemostatic Process #1**

- Hemorrhage
- Vascular endothelial damage
- Blood flow

**Hemostatic Process #2**

- Platelet
- Activated platelet
- "Unstable" platelet plug
- Blood flow
- Vascular endothelial damage

**Hemostatic Process #3**

- Coagulation cascade
- Fibrin
- Cross-linked fibrin
- Blood flow
- Vascular endothelial damage

**Hemostatic Process #4**

- Cross-linked fibrin
- Degradation products
- Fibrinolytic system
- Blood flow
- Vascular endothelial damage

**Hemostatic Process #5**

- Healed vascular endothelium
Vessel Injury

Collagen Exposure

Platelet Adhesion and Release Reaction

- Thromboxane A2, ADP

Platelet Aggregation

- Reduced blood flow
- Primary Hemostatic Plug
- Platelet fusion

Blood coagulation cascade

- Thrombin
- Fibrin

Tissue Factor

Platelet phospholipid

Stable haemostatic plug

Vasoconstriction